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July 28, 2000

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VIA OVERNIGHT DELIVERY

Dockets Management Branch
Food and Drug Administration [HFA-305]
Department of Health and Human Services
Room 1061
5630 Fishers Lane
Rockville, Maryland 20852

Re: **Docket No. 00P-0499**

The undersigned, on behalf of Apotex, Inc., the TorPharm Division of Apotex, Inc. and Apotex Corporation (collectively, "Apotex"), submit this reply to the June 13, 2000 response ("Response") of counsel for SmithKline Beecham Corp. ("SmithKline") regarding Apotex's Citizen Petition for relief from the anticompetitive effects of certifying to patents improperly listed in the Orange Book with approved New Drug Application ("NDA") No. 020-031 for crystalline paroxetine hydrochloride hemihydrate. Even if FDA declines to analyze claims within patents, FDA should de-list the patents in issue, because, contrary to SmithKline's argument (Response at 7), the attached declarations do not comply with FDA regulations for supporting patent listings.

Patent listing is crucial to maintaining the Hatch-Waxman Amendments' balance that Congress established to protect innovators' inventions while encouraging generic manufacturers to provide marketplace access to lower cost, safe, and effective generic drugs. *See* Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, Tit. I, 98 Stat. 1585 (1984)(codified as amended 21 U.S.C. §355, hereinafter, "the Act"). Each listed patent potentially extends for 30 months monopoly control and marketplace dependence on one source of a safe and effective drug. *See* 21 U.S.C. §355(j)(5). SmithKline has incentives to preserve its monopoly and improperly has submitted in serial fashion additional patent information to FDA. Indeed, while this Citizen Petition has been pending, SmithKline submitted, and FDA listed, an additional

patent for NDA 020-031. Response at 9, n. 32. SmithKline's serial patent submission tactics and FDA's lapses in enforcing both the Act and its own regulations threaten to postpone indefinitely public access to the benefits of competitive generic drugs.

No Dispute: The Late Patents Do Not Claim The NDA Drug

The Act limits listed patents to those which claim the NDA drug. 21 U.S.C. §355(b)(1). Perhaps Apotex, FDA, and SmithKline dispute appropriate procedural remedies and scope of discretion, but there is no dispute here that the challenged patents do not claim the approved NDA drug.

SmithKline admits, as it must, that FDA approved NDA 020-031 for crystalline paroxetine hydrochloride *hemihydrate*. Response at 6. The Orange Book for NDA 020-031 lists U.S. Patent No. 4,721,723 ("the '723 hemihydrate patent"), which claims "crystalline paroxetine hydrochloride hemihydrate."[1] SmithKline improperly argues (Response at 5) that its approved NDA drug is broader -- paroxetine hydrochloride, apparently in all forms -- than the claim of the '723 hemihydrate patent. The Act, however, does not permit SmithKline to broaden its anti-competitive shield beyond the precise claim of its '723 hemihydrate patent and the precise drug that FDA approved. The approved NDA drug and the '723 hemihydrate patent are limited to crystalline paroxetine hydrochloride *hemihydrate*, and FDA should not list in the Orange Book any patents which claim any other drug, regardless of whether or not the drug includes in its name the words "paroxetine hydrochloride."[2]

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[1] The '723 hemihydrate patent also describes the initial predecessor patent, U.S. Patent No. 4,007,196 ("the '196 patent"), which generally discloses paroxetine hydrochloride. *See* Tab A to February 4, 2000 Citizen Petition at col. 1. The '196 patent has expired. FDA has not approved paroxetine hydrochloride in any form other than crystalline paroxetine hydrochloride hemihydrate, for which SmithKline submitted the '723 patent.

[2] SmithKline attempts to place form over substance by arguing (Response at 5-6) that the title on FDA-approved labeling and in the Orange Book suggests that the approved drug which patents must claim is merely "paroxetine hydrochloride." But the FDA approved labeling, beyond the title, states that the approved drug is paroxetine hydrochloride *hemihydrate*, which remains the approved NDA drug, regardless of how the Orange Book labels the active ingredient.

There is no dispute that the challenged patents, U.S. Patent No. 5,872,132 ("the '132 Form C patent") and U.S. Patent No. 5,900,423 ("the '423 Form A patent"), do not claim the approved NDA drug; rather, the later patents claim forms of paroxetine hydrochloride *anhydrate*. FDA has not yet approved a paroxetine hydrochloride anhydrate product for human use. SmithKline may not market, and has not sought FDA approval to market, the paroxetine hydrochloride anhydrate that the '132 Form C and the '423 Form A patents claim.

Apotex presents the American public with the first opportunity to obtain the benefits of a safe, effective, and low cost paroxetine hydrochloride anhydrous drug, because Apotex was the first company to submit an abbreviated new drug application ("ANDA"), under 21 U.S.C. §355(j), which referenced NDA 020-031. Apotex, not SmithKline, has developed and submitted the data that will enable FDA to approve a paroxetine hydrochloride anhydrous drug for human use.

Apotex's ANDA efforts fulfill Congressional intent for the Act, notwithstanding SmithKline's improper argument (Response at 6) that attempts to ignore the Act's distinctions between standards for ANDA approval and for patent listing. SmithKline asserts incorrectly that it should be able to list, with an approved NDA, patents which merely claim the same active ingredient or a bioequivalent drug, and argues that it may do so because FDA may approve ANDAs for drugs with the same active ingredient and which are bioequivalent to an NDA drug. Response at 6. Contrary to SmithKline's assertions (Response at 6), it is more than "conceivable," Congress expressly established a balance in the Act by limiting Orange Book listings to those patents which claim the approved NDA drug and by simultaneously authorizing FDA to approve ANDAs for bioequivalent products with the same active ingredient -- concepts for which FDA has established separate standards. *Compare* 21 U.S.C. §355(b)(1) *with* 21 U.S.C. §355(j)(2)(A)(ii), (iv); *see also*, *Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998)(the Act grants FDA discretion to approve an ANDA that differs in chemical structure from an NDA, if difference is clinically irrelevant). The Act simply does not allow SmithKline to extend market exclusivity benefits for an approved NDA

drug by submitting patents which claim different unapproved chemical forms of the *active ingredient* of that specific approved NDA drug.

The Act does not grant authority to extend monopolies by listing patents which do not claim an approved NDA drug, but SmithKline nonetheless argues that it is entitled to extend its monopoly. Response at 6. SmithKline, however, misdirects concern about generic manufacturers' efforts to "piggyback" on SmithKline data, because Congress acted to prevent SmithKline from being piggy in the market. Congress balanced interests in the Act by allowing innovators exclusive rights to the approved NDA drug which a patent claims, but also encouraged competition by allowing FDA to approve generic innovations which design bioequivalent products to avoid patent claims. Congressional intent for ANDA approval corresponds to traditional encouragement for innovators who design products to avoid patent claims. *See Westvaco Corp. v. International Paper Co.*, 991 F.2d 735, 745 (Fed. Cir. 1993)("keeping track of a competitor's products and designing new and possibly better or cheaper functional equivalents is the stuff of which competition is made and is supposed to benefit the consumer"); *London v. Carson Pirie Scott & Co.*, 946 F.2d 1534, 1538 (Fed. Cir. 1991)("designing or inventing around patents to make new inventions is encouraged").

SmithKline thus far has benefitted from FDA's improper application of the Act by obtaining listings of patents, *after* ANDA filings, which claim, at best, bioequivalent -- not FDA-approved -- drugs. Each new patent listing has enabled SmithKline improperly to extend its monopoly in a manner contrary to Congressional intent. SmithKline should not be able to use patents, which claim unapproved drugs that SmithKline does not intend to market, solely for the purpose of preserving monopoly power by blocking approval of safe, effective, and low cost generic products.

FDA Listed Patents Pursuant To Facially Deficient Declarations

The Act and the undisputed facts establish that the '132 Form C and '423 Form A patents do not claim the approved NDA drug and should not have been listed in the Orange Book. However, FDA has asserted that it cannot and need not analyze patent claims (although Apotex respectfully disagrees, as described in prior submissions). Moreover, FDA asserts that it need not correct the problem and that the matter should be

left to private litigants such as Apotex and SmithKline to resolve in court (again, Apotex respectfully disagrees).

Regardless of FDA's position on analyzing patent claims and correcting improper listings, FDA has promulgated a regulation which tracks the Act by requiring NDA holders to declare that additional submitted patents claim the approved NDA drug. 21 C.F.R. §314.53(c)(2). SmithKline argues (Response at 7) that its declarations for the '132 Form C and '423 Form A patents comply with the declaration regulation. SmithKline is wrong. FDA need not accept Apotex's word for this, because the deficient declarations, which became available to Apotex during the course of this dispute, are attached to this reply for FDA's further review.

A review of the attached declarations suggests that SmithKline simply made no effort to comply with FDA's regulation, because the declarations fail to state that the '132 Form C and '423 Form A patents claim the approved crystalline paroxetine hydrochloride hemihydrate drug. Thus, SmithKline's declarations presented FDA with a fair opportunity to follow its own regulations and to reject SmithKline's request to list the '132 Form C and '423 Form A patents in the Orange Book with NDA 020-031. FDA, however, inexplicably listed the '132 Form C and '423 Form A patents, despite the facially deficient declarations, which fail to comply with FDA's own regulation.

FDA should correct its oversight, which resulted in patent listings to the detriment of competition. Apotex knows of (but disagrees with) FDA's position that FDA does not analyze patent claims, but Apotex believes that the American public reasonably should be able to depend upon FDA to review and to reject declarations that do not meet requirements that FDA established to relieve itself of the burden of analyzing patent claims. 21 C.F.R. §314.53(c)(2).

Apotex further knows (but will continue to challenge) FDA's regulation for correcting improperly listed patent information, 21 C.F.R. §314.53(f), but that regulation does not apply to correct the administrative lapse which led to the failure to reject the facially deficient declarations. SmithKline inappropriately attempts to avoid FDA scrutiny by arguing (Response at 1) that FDA has rendered itself powerless to correct the patent listing errors in issue here. Apotex properly through this process draws FDA's

attention to the improper declarations that FDA should not have accepted, because FDA at least retains the authority to determine that the declarations which supported patent listing are defective and to grant relief associated with that determination.

FDA has an opportunity through this process to correct an oversight which significantly impacts competition. FDA allowed patents to be listed[3], despite declarations that do not comply with FDA regulations or the Act. Apotex requests that FDA grant its Citizen Petition and issue directions sufficient to provide the relief requested.

The matters at issue in this Citizen Petition are causing irreparable harm to Apotex and remain the subject of pending litigation. Apotex thus renews its request for an expedited determination of this Citizen Petition.

Sincerely,

LORD, BISSELL & BROOK

By: Terrence P. Canade

cc: Bruce N. Kuhlik -- Covington & Burling

[3] Apotex has yet to obtain access to the requisite declaration that SmithKline had to present to FDA to enable FDA to list the latest patent, U.S. Patent No. 6,063,927. That patent does not claim crystalline paroxetine hydrochloride hemihydrate, and therefore Apotex does not believe that SmithKline truthfully could have submitted a declaration that complies with 21 C.F.R. §314.53(c)(2).

SmithKline Beecham

Charles M. Kinzig
Vice President and Director
Corporate Intellectual Property - U.S.

March 12, 1999

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Building, Room 2-14
12420 Parklawn Drive
Rockville, Maryland 20857

Re: **NDA No. 20-031**
NDA No. 20-710
NDA No. 20-885
NDA No. 20-936
Time Sensitive Patent Information

Dear Sirs:

In accordance with 21 C.F.R. 314.53, SB submits the following patent information relating to the subject NDAs. The following patent covers paroxetine hydrochloride anhydrate, which under current FDA policy is considered "the same active ingredient" as paroxetine hydrochloride hemihydrate, the active ingredient of *Paxil* (paroxetine hydrochloride).

Patent Number	Expiration Date	Type of Patent	Patent Owner	Representative of Patent Owner
5,872,132	5/19/15	Drug Substance and Drug Product	SmithKline Beecham Corporation	Charles M. Kinzig, Corporate Intellectual Property – U.S., Mail Code UW2220 SmithKline Beecham Corporation 709 Swedeland Road King of Prussia, PA 19406

The undersigned declares that U.S. Patent Number 5,872,132 covers the formulation, composition and method of use of Paroxetine Hydrochloride Tablets, Paroxetine Hydrochloride Oral Suspension, Paroxetine Hydrochloride Capsules and Paroxetine Hydrochloride Controlled Release Tablets. These products are currently approved under Section 505 of the Federal Food, Drug and Cosmetic Act.

This letter is being submitted in duplicate.

Very truly yours,

Charles M. Kinzig

SB01001-067048
Confidential
Subject To Protective Order

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Internet: Charles_M_Kinzig@SBPHRD.com

SmithKline Beecham

Charles M. Kinzig
[illegible]

May 13, 1999

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Building, Room 2-14
12420 Parklawn Drive
Rockville, Maryland 20857

Re: NDA No. 20-031
Time Sensitive Patent Information

Dear Sirs:

In accordance with 21 C.F.R. 314.53, SB submits the following patent information relating to the subject NDA. The following patent covers paroxetine hydrochloride anhydrate, which under current FDA policy is considered "the same active ingredient" as paroxetine hydrochloride hemihydrate, the active ingredient of *Paxil* (paroxetine hydrochloride).

Patent Number	Expiration Date	Type of Patent	Patent Owner	Representative of Patent Owner
5,900,423	5/19/15	Drug Substance and Drug Product	SmithKline Beecham Corporation	Charles M. Kinzig, Corporate Intellectual Property – U.S.. Mail Code UW2220 SmithKline Beecham Corporation 709 Swedeland Road King of Prussia, PA 19406

The undersigned declares that U.S. Patent Number 5,900,423 covers the formulation, composition and/or method of use of Paroxetine Hydrochloride Tablets. This product is currently approved under Section 505 of the Federal Food, Drug and Cosmetic Act.

This letter is being submitted in duplicate.

Very truly yours,

Charles M. Kinzig

[illegible]
MAY 14 1999

SB01001-065689
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